Patent
Attorney's Docket No. 030560-056

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Andreas BERNKOP-SCHNURCH

Application No.: 09/830,986

Filed: April 20, 2001

For: MUCO-ADHESIVE POLYMERS, USE THEREOF AND METHOD FOR PRODUCING THE SAME

Group Art Unit: 1619

Examiner: M. Willis

DECLARATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Andreas Bernkop-Schnurch, Ph.D., hereby declare as follows:

1. I am the named inventor for the above-identified application.

2. My Curriculum Vitae is attached hereto as Appendix A.

3. I am a person of at least ordinary skill in the art of mucoadhesives.

4. I have read the instant application as well as the Official Action dated March 27, 2002, and Constancis et al, U.S. Patent No. 5,496,872, which is cited therein.

5. I do not agree with the assertions in the Official Action that the instantly claimed invention is disclosed by or obvious in view of Constancis et al, U.S. Patent No. 5,496,872, or is obvious in view of Bernkop-Schnurch in combination with Constancis.

6. The instant invention relates to mucoadhesive polymers having improved properties. The improved mucoadhesive polymers "enable a targeted introduction of active substance in mucus layers, wherein a stable presence at the target site shall be enabled."

By this invention, an effective and efficient active substance delivery system is provided "by which an improved and thus also extended adhesion of drug on the mucosae can be attained." Page 2, ¶2, of the application.

7. The term "mucoadhesive" is recognized in the art. It is a term of art that is used to describe a particular class of polymers. U.S. Patent No. 5,047,244, for example, defines "mucoadhesive"as being "a material that adheres to a mucosal tissue surface in-vivo and/or in-vitro. Such adhesion will adherently localize the dosage form onto the mucus membrane and requires the application of a force of at least about 50 dynes/cm^2 to separate the mucoadhesive material from the mucus membrane." Col. 3, lns. 21-27.

8. The term "mucoadhesive," as used herein, is a polymer that adheres to the mucus layer covering a mucosal tissue surface in-vivo and/or in-vitro. Such adhesion has to be higher than at least 83 μJ for the total work of adhesion (TWA) described for tensile studies with dry compacts, according to Bernkop-Schnürch et al. *Pharm. Res.* 16, 1999, 876-881.

9. Mucoadhesive polymers are recognized in the art as including polyacrylates, (e.g., carbomer, polycarophil, carbopol, etc.), cellulose derivatives (e.g., sodium carboxymethylcellulose, hydroxypropylcelulose, etc.), hyaluronic acid, alginate, pectin and chitosan. *See, e.g.*, Bernkop-Schnürch, A. (2002). *Mucoadhesive Polymers In: Polymeric Biomaterials* 2nd edition (Ed. Severian Dumitriu) Marcel Dekker, New York.

Hagerstrom H, Edsman K. "Interpretation of mucoadhesive properties of polymer gel preparations using a tensile strength method." *J Pharm Pharmacol* 2001 Dec; 53(12):1589-99

Eouani C, Piccerelle P, Prinderre P, Bourret E, Joachim J. "In-vitro comparative study of buccal mucoadhesive performance of different polymeric films." *Eur J Pharm Biopharm* 2001 Jul; 52(1):45-55;

Singla AK, Chawla M, Singh A. "Potential applications of carbomer in oral mucoadhesive controlled drug delivery system: a review." *Drug Dev Ind Pharm* 2000 Sep; 26(9):913-24;

Kerec M, Bogataj M, Mugerle B, Gasperlin M, Mrhar A. "Mucoadhesion on pig vesical mucosa: influence of polycarbophil/calcium interactions." *Int J Pharm* 2002 Jul 8; 241(1):135-43;

Solomonidou D, Cremer K, Krumme M, Kreuter J. "Effect of carbomer concentration and degree of neutralization on the mucoadhesive properties of polymer films." *J Biomater Sci Polym Ed* 2001;12(11):1191-205;

Adriaens E, Remon JP, Ludwig A. "Evaluation of a mucoadhesive tablet for ocular use." Ceulemans J, Vermeire A, *J Control Release* 2001 Dec 13; 77(3):333-44;

Bernkop-Schnurch A, Gilge B., "Anionic mucoadhesive polymers as auxiliary agents for the peroral administration of (poly)peptide drugs: influence of the gastric juice." *Drug Dev Ind Pharm.* 2000 Feb; 26(2):107-13.

10. Constancis does not disclose or suggest "mucoadhesive" polymers, as instantly claimed. Constancis instead relates to "biocompatible and biodegradable surgical adhesives based on non-toxic products." Col. 1, lns. 39-42. More specifically, Constancis discloses biological "glues or gluing material." Col. 5, lns. 24-25. It is obvious that

nobody would use a surgical adhesive to try to connect one mucus gel layer with another, or to try to connect a mucus gel layer with a tissue.

11. The bioadhesives of Constancis are not "mucoadhesives." This would be apparent to a person skilled in the art. For example, Constancis' bioadhesives would not adhere to the mucosa with the same strength as a mucoadhesive polymer, for example, as taught by the '244 Patent. This is because they do not fulfill the minimal criteria to be mucoadhesive. For instance, in the teaching book *Drug Delivery Systems* (Ellis Horwood, New York), G. Hunt, P. Kearney and I. Kellaway defined criteria for polymers to be mucoadhesive in the chapter "Mucoadhesive polymers in drug delivery systems" as follows:

- Strong H-bonding groups (-OH, -COOH)
- Strong anionic charges
- Sufficient flexibility to penetrate the mucus network
- Surface tension characteristics suitable for wetting mucus/mucosal tissue surfaces
- High molecular weight

In contrast to the mucoadhesive polymers mentioned in ¶8 *supra* and also as claimed in my patent application, not even a single point out of these five is fulfilled by the monomers/polymers described by Constancis.

12. My invention relates to the surprising discovery that by introducing at least one non-terminal thiol group into a mucoadhesive polymer having not more than 10 different monomers, the mucoadhesive properties of the polymer are greatly improved.

This discovery was unexpected. I discovered that the mucoadhesive polymers having the non-terminal thiol group could form reversible, covalent bonds with the cysteine-rich subdomains of the mucus glycoproteins (*see,* Figure 1 of the application). These bonds allow for a stable localization of the polymers on the mucus layer of certain mucosal membranes. *See also,* page 3 of the application.

13. Unexpectedly, the mucoadhesive polymers of my invention have significantly improved binding capacity to intestinal mucosa. As stated *supra*, the most frequently used mucoadhesive polymers are polymers such as mentioned in claim 3 of the instant application, *e.g.*, polyacrylates (Carbomer, Polycarbophil, Carbopol, *etc.*), cellulose derivatives (sodium carboxymethylcellulose, hydroxypropylcellulose, *etc.*), hyaluronic acid, alginate, pectin and chitosan.

14. In the following table the mucoadhesive properties of these polymers is listed. In addition, the improvement in the mucoadhesive properties of these polymers by the immobilization of thiol groups is shown as well.

Polymer	**Total work of adhesion in μJ; means ± SD (n= 3-8)**	**Reference**
polycarbophil		A. Bernkop-Schnürch, V. Schwarz, S. Steininger, Polymers with thiol groups: a new generation of mucoadhesive polymers? Pharm. Res. 16 (1999) 876-881.
thiolated polycarbophil	280 ±68	
sodium carboxymethyl cellulose	108 ±17	A. Bernkop-Schnürch, S. Steininger, Synthesis and characterisation of

		mucoadhesive thiolated polymers, Int. J. Pharm. 194 (2000) 239-247.
thiolated sodium carboxymethyl cellulose	157 ±6	
chitosan HCl	23 ±10	C.E. Kast, A. Bernkop-Schnürch, Thiolated polymers: development and in vitro evaluation of chitosan-thioglycolic acid conjugates, Biomaterials 22 (2001) 2345-2352.
thiolated chitosan	234 ±0	
sodium alginate	26 ±1	A. Bernkop-Schnürch, C.E. Kast, M.F. Richter, Improvement in the mucoadhesive properties of alginate by the covalent attachment of cysteine, J. Control. Release 71 (2001) 277-285.
thiolated sodium alginate	102 ±36	

15. This strong improvement in the mucoadhesive properties was unexpected. It is based on thiol/disulfide exchange reactions between the polymer and the mucus layer. Prior to my invention, there was nothing reported in the literature about thiolated mucoadhesive polymers. This can be documented by the reviewer's report of the first publication submitted about thiolated mucoadhesive polymers. In the top-journal for this research field (*Pharmaceutical Research*) it is written about a "brilliant idea."

16. In addition, nothing is reported about this mechanism by Constancis et al.

17. I believe that the instant invention is truly novel. The improved properties of the mucoadhesive polymers I found were not suggested in the art generally, or more specifically in Constancis.

18. I further declare that I am aware that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and my jeopardize the validity of any patent application or any patent issuing thereon. All statements made of my own knowledge are true, and all statements made on information and belief are believed to be true.

_____ _____

Date Andreas Bernkop-Schnurch, Ph.D.

Curriculum vitae

Name: Univ.-Prof. Dr. Andreas BERNKOP SCHNÜRCH
Current address: A-1050 Vienna, Christophg.6/11
Born: 1965 12 06 in Klagenfurt
Nationality: Austrian
Marital status: single

May 2002	Offer for the Chair in Pharmaceutical Technology and Biopharmaceutics, Leopold-Franzens-Universität, Innsbruck
February 2002	First position in the ranking for the Chair in Pharmaceutical Technology and Biopharmaceutics, Leopold-Franzens-Universität, Innsbruck, Austria
April 2001	Offer for the C3-Professur, Institute of Pharmaceutical Technology and Biopharmaceutics, Ludwig-Maximilians-University, Munich, Germany
June 2000	Offer for the Chair in Pharmaceutics, School of Pharmacy, University of London
since March 1999	Associate Professor, permanent position at the Institute of Pharmaceutical Technology and Biopharmaceutics, University of Vienna
Nov. 1998	Habilitation for Pharmaceutical Technology, University of Vienna
April 1998	Second position in the ranking for the Chair in Pharmaceutical Technology and Biopharmaceutics (C4-Professor), Ludwig-Maximilians-University, Munich, Germany
May 1996	Proof of qualification for the wholesale trade of drugs
since 1994	Reader for: 'Peptide and Protein Drugs' 'Manufacturing of Cosmetics' and 'Manufacturing of Dosage Forms'
Oct. 1993 - May 1994	Military service
April 1994	Graduation as doctor for natural sciences at the University of Vienna
June 1991 - Oct. 1992	Scientific work at the Institute of Microbiology and Genetics, University of Vienna
since March 1991	Employment as 'University Assistant' at the Institute of Pharmaceutical Technology, University of Vienna
1990-1991	Practicing at a pharmacy in Vienna
Feb. 1990	Master degree at the University of Vienna
1984-1990	Study of pharmacy at the University of Vienna
1976-1984	Secondary school (Bundesgymnasium, St. Veit/Glan) -stress on natural science
1972-1976	Public primary school in St. Veit/Glan

Andreas BERNKOP-SCHNÜRCH

Date of birth: 6/12/1965
Position: Professor at the Institute of Pharmaceutical Technology and Biopharmaceutics, University of Vienna
Address: Institute of Pharmaceutical Technology and Biopharmaceutics, University of Vienna
Althanstraße 14, A-1090 Vienna, Austria
Tel.: ++43 1 4277 55413
Fax: ++43 1 4277 9554
E-mail: Andreas.Bernkop-Schnuerch@univie.ac.at

Research field: Development of drug delivery systems

(Poly)peptide drug delivery systems
Enzyme-inhibitors as auxiliary agents
Mucoadhesive polymers
Permeation enhancement
Sustained release systems
Evaluation of drug absorption from mucosal tissues
Evaluation of the presystemic metabolism of orally given drugs

Original research articles

1. Bernkop-Schnürch*, A., Gabor, F., Szostak, M.P., and Lubitz, W. (1995). An adhesive drug delivery system based on K99-fimbriae. *Eur. J. Pharm. Sci.* **3**, 293-299.

2. Bernkop-Schnürch*, A., Gabor, F., Szostak, M.P., and Lubitz, W. (1995). Production of adhesive drug carriers using recombinant DNA-technology. *Sci. Pharm.* **63**, 159-166.

3. Bernkop-Schnürch*, A., Valenta, C., and Urban, U. (1995). Microbiological Stability of Individually Prepared Dermatica. *Sci. Pharm.* **63**, 65-70.

4. Bernkop-Schnürch*, A., and Valenta, C. (1995). Untersuchungen zur mikrobiellen Stabilität von magistral hergestellten hydrophilen Cremes und Gelen. *ÖAZ* **49**, 926-929.

5. Bernkop-Schnürch*, A., and Dundalek, K. (1996). Novel bioadhesive drug delivery system protecting (poly)peptides from gastric enzymatic degradation. *Int. J. Pharm.*, **138**, 75-83.

6. Bernkop-Schnürch*, A., Valenta, C., and Gatterwe, V. (1996). *In vitro* skin permeation studies of the lantibiotic nisin. *Eur. J. Pharm. Biopharm.*, **42**, 336-339.

7. Bernkop-Schnürch*, A. and Fragner, R. (1996). Investigations into the diffusion behaviour of polypeptides in native intestinal mucus with regard to their peroral administration. *Pharm. Sciences* **2**, 361-363.

8. Bernkop-Schnürch*, A., Paikl, Ch., and Valenta, C. (1997). Novel Bioadhesive Chitosan-EDTA Conjugate Protects Leucine Enkephalin from Degradation by Aminopeptidase N. *Pharm. Res.* **14**, 917-922.

9. Bernkop-Schnürch*, A., and Göckel, N.C. (1997). Development and analysis of a polymer protecting from luminal enzymatic degradation caused by α-chymotrypsin. *Drug Dev. Ind. Pharm.*, **23**, 733-740.

10. Bernkop-Schnürch*, A., and Apprich, I. (1997). Synthesis and evaluation of a modified mucoadhesive polymer protecting from α-chymotrypsinic degradation. *Int. J. Pharm.*, **146**, 247-254.

11. Bernkop-Schnürch*, A., and Marschütz, M. (1997). Development and *in vitro* evaluation of systems to protect peptide drugs from aminopeptidase N. *Pharm. Res.*, **14**, 181-185.

12. Bernkop-Schnürch*, A., Schwarz, G.H., and Kratzel M. (1997). Modified Mucoadhesive Polymers for the Peroral Administration of Mainly Elastase Degradable Therapeutic (Poly)peptides. *J. Control. Release,* **47**, 113-121.

13. Bernkop-Schnürch*, A., Gabor, F., and Spiegl, P. (1997). Bacterial adhesins as a drug carrier: covalent attachment of K99 fimbriae to 6-methylprednisolone. *Pharmazie*, **52**, 41-44.

14. Bernkop-Schnürch*, A., Bratengeyer, I., and Valenta, C. (1997). Development and in vitro evaluation of a drug delivery system protecting from trypsinic degradation. *Int. J. Pharm.*, **157**, 17-25.

15. Bernkop-Schnürch*, A., and Krajicek, M.E. (1998). Mucoadhesive polymers as platforms for peroral peptide delivery and absortion: synthesis and evaluation of different chitosan-EDTA conjugates. *J. Control. Release,* **50**, 215-223.

16. Bernkop-Schnürch*, A., Krist, S., Vehabovic, M., and Valenta, C. (1998). Synthesis and evaluation of lysozyme derivatives exhibiting an enhanced antimicrobial action. *Eur. J. Pharm. Sciences,* **6**, 303-309.

17. Bernkop-Schnürch*, A., and Scerbe-Saiko, A. (1998). Synthesis and *in Vitro* Evaluation of Chitosan-EDTA-Protease-Inhibitor Conjugates which might be useful in Oral Delivery of Peptides and Proteins. *Pharm. Res.*, **15**, 263-269.

18. Bernkop-Schnürch*, A., Humenberger, C., and Valenta, C. (1998). Basic Studies on Bioadhesive Delivery Systems for Peptide and Protein Drugs. *Int. J. Pharm.*, **165**, 217-225.

19. Bernkop-Schnürch*, A., and Pasta, M. (1998). Intestinal Peptide and Protein Delivery: Novel Bioadhesive Drug Carrier Matrix Shielding from Enzymatic Attack. *J. Pharm. Sci.*, **87**, 430-434.

20. Bernkop-Schnürch*, A., Krauland, A., and Valenta, C. (1998). Development and *in vitro* Evaluation of a Drug Delivery System based on Chitosan-EDTA BBI Conjugate. *J. Drug Targ.*, **6**, 207-214.

21. Bernkop-Schnürch*, A. and Freudl, J. (1999). Comparative *in vitro* Study of Different Chitosan-Complexing Agent Conjugates. *Pharmazie*, **54**, 369-371.

22. Bernkop-Schnürch*, A., Schwarz, V., and Steininger, S. (1999). Polymers with Thiol Groups: A New Generation of Mucoadhesive Polymers? *Pharm. Res.*, **16**, 876-881.

23. Bernkop-Schnürch*, A., Kirchmayer, R. and Kratzel, M. (1999). Synthesis, Development and in vitro Evaluation of Drug Delivery Systems with Protective Effect Towards Pepsinic Degradation. *J. Drug Targ.*, **7**, 55-63.

24. Bernkop-Schnürch*, A., Valenta, C., and Daee, S.M. (1999) Peroral polypeptide delivery: A comparative *in vitro* study of mucolytic agents. *Arzneimittelforschung.*, **49**, 799-803.

25. Bernkop-Schnürch*, A., Brandt U.-M., and Clausen, A. (1999) Synthese und *in vitro* Evaluierung von Chitosan-Cystein Konjugaten. *Sci. Pharm.*, **67**, 197-208.

26. Bernkop-Schnürch*, A. and Thaler, S. (2000). Polycarbophil-Cysteine Conjugates as Platforms for Oral (Poly)peptide Delivery Systems. *J. Pharm. Sci.*, **89**, 901-909.

27. Bernkop-Schnürch*, A. and Steininger, S. (2000) Synthesis and Characterisation of Mucoadhesive Thiolated Polymers. *Int. J. Pharm.*, **194**, 239-247.

28. Bernkop-Schnürch*, A. and Gilge, B. (2000). Anionic mucoadhesive polymers as auxiliary agents for the peroral administration of (poly)peptide drugs: influence of the gastric fluid. *Drug Dev. Ind. Pharm.*, **26**, 107-113.

29. Bernkop-Schnürch*, A., Giovanelli, R., and Valenta, C. (2000). Peroral Administration of Enzymes: Strategies to Improve the Galenic of Dosage Forms for Trypsin and Bromelain. *Drug Dev. Ind. Pharm.*, **26**, 115-121.

30. Bernkop-Schnürch*, A., Scholler, S., and Biebel, R.G. (2000). Development of Controlled Drug Release Systems Based on Polymer-cysteine Conjugates. *J. Control. Release*, **66**, 39-48.

31. Bernkop-Schnürch*, A., Clausen, A.E., and Hnatyszyn, M. (2001) Thiolated Polymers: Synthesis and in vitro evaluation of polymer-cysteamine conjugates. *Int. J. Pharm.*, **226**, 185-194.

32. Bernkop-Schnürch*, A., Kast, C.E., and Richter, M.F. (2001) Improvement in the mucoadhesive properties of alginate by the covalent attachment of cysteine. *J. Control. Release*, **71**, 277-285.

33. Bernkop-Schnürch*, A., Zarti, H., and Walker, G.F. (2001) Thiolation of polycarbophil enhances its inhibition of soluble and intestinal brush border membrane bound aminopeptidase N. *J. Pharm. Sci.*, 90, 1907-1914.

34. Bernkop-Schnürch*, A. and Hopf, Th.E. (2001) Synthesis and *In vitro* evaluation of chitosan-thioglycolic acid conjugates. *Sci. Pharm.*, **69**, 109-118.

35. Bernkop-Schnürch*, A., Schuhbauer H., Clausen, A.E. and Hanel, R. (2002) Development of a Sustained Release Dosage Form for α-Lipoic Acid: Design and in Vitro Evaluation. *Drug Dev. Ind. Pharm.*, under review.

36. Bernkop-Schnürch*, A., Reich-Rohrwig, E., Marschütz, M., Schuhbauer H. and Kratzel, M. (2002) Development of a Sustained Release Dosage Form for α-Lipoic Acid: Evaluation in Human Volunteers. *Drug Dev. Ind. Pharm*, under review.

37. Bernkop-Schnürch*, A., König, V. Leitner, V. and Brodnik, I. (2002) The Preparation and Characterisation of Mucoadhesive Thiolated Poly(methacrylic acid) - Starch Compositions. *Eur. J. Pharm. Biopharm.*, under review.

38. Bernkop-Schnürch*, A., Hornof, M. and Zoidl, T. (2002) Thiolated polymers – thiomers: modification of chitosan with 2-iminothiolane, *Biomaterials*, under review.

39. Clausen, A.E., and Bernkop-Schnürch*, A. (2000) *In Vitro* Evaluation of the Permeation-Enhancing Effect of Thiolated Polycarbophil. *J. Pharm. Sci.,* **89**, 1253-1261.

40. Clausen, A.E., and Bernkop-Schnürch*, A. (2001) Development and *in Vitro* Evaluation of a Peptide Drug Delivery System Based on Thiolated Polycarbophil. *Pharm. Ind.*, **63**, 312-317.

41. Clausen, A.E., and Bernkop-Schnürch*, A. (2001) Thiolated Carboxy-methylcellulose: *In vitro* evaluation of its permeation enhancing effect on peptide drugs. *Eur. J. Parm. Biopharm.*, **51**, 25-32.

42. Clausen, A.E., and Bernkop-Schnürch*, A. (2001) Direct compressible polymethacrylic acid-starch compositions for site specific drug delivery. *J. Controlled Release*, **75**, 93-102.

43. Clausen, A.E., Kast, C.E. and Bernkop-Schnürch*, A. (2002) The role of glutathione in the permeation enhancing effect of thiolated polymers. *Pharm. Res.*, **19**, 602-608.

44. Gabor*, F., Bernkop-Schnürch, A., and Hamilton, G. (1997) Bioadhesion to the intestine by means of *E. coli* K99-fimbriae: Gastrointestinal stability and specificity of adherence. *Eur. J. Pharm. Sci.*, **5**, 233-242.

45. Hornof, M.D., Kast, C.E., and Bernkop-Schnürch*, A. (2002). In vitro evaluation of the in situ gelling behavior of chitosan - thioglycolic acid conjugates. *Eur J. Pharm . Biopharm.*, under review.

46. Hornof M.D. and Bernkop-Schnürch*, A. (2002). Ex vivo evaluation of the permeation enhancing effect of polycarbophil - cysteine conjugates on the cornea of rabbits. *J. Pharm. Sci.* in press.

47. Kast, C.E., and Bernkop-Schnürch*, A. (2001). Thiolated polymers: development and in vitro evaluation of chitosan-thioglycolic acid conjugates. *Biomaterials*, **22**, 2345 - 2352.

48. Kast, C.E., and Bernkop-Schnürch*, A. (2002). Polymer-cystamine conjugates: new mucoadhesive excipients for drug delivery? *Int. J. Pharm.*, **234**, 91-99.

49. Kast, C.E., Frick, W., Losert, U. and Bernkop-Schnürch*, A. (2002) Chitosan-Thioglycolic acid conjugate: A new scaffold material for tissue engineering? *Int. J. Pharm.*, under review.

50. Kast, C.E., Valenta*, C., Leopold, M. and Bernkop-Schnürch, A. (2002) Design and in vitro evaluation of a novel bioadhesive vaginal drug delivery system for clotrimazole. *J. Control. Rel.*, **81**, 347-354.

51. Kast, C.E., Guggi, D., Langoth, N. and Bernkop-Schnürch*, A. (2002) Development and in vivo evaluation of an oral delivery system for low molecular weight heparin based on thiolated polycarbophil. *Pharm. Res*, under review.

52. Kast, C.E. and Bernkop-Schnürch*, A. (2002) Influence of the molecular mass on the permeation enhancing effect of different poly(acrylates). *STP pharma*, in press.

53. Kopp*, B., Bauer, W.P., and Bernkop-Schnürch, A. (1992). Analysis of some Malaysian dart poisons. *J. Ethnopharmacol.*, **36**, 57-62.

54. Kratzel*, M., Hiessböck, R., and Bernkop-Schnürch, A. (1998). Auxiliary Agents for the Peroral Administration of Peptide and Protein Drugs: Synthesis and Evaluation of Novel Pepstatin Analogues. *J. Med. Chem.*, **41**, 2339-2344.

55. Kratzel*, M., Schlichtner, B., Kirchmayer, R. and Bernkop-Schnürch, A. (1998). Simplified Pepstatins: Synthesis and Evaluation of *N*-Terminally Modified Analogues. *J. Med. Chem.*, **42**, 2041-2045.

56. Kratzel*, M. and Bernkop-Schnürch, A. (2000). Valaminols, probably the most simplified peptide-analogs acting as pepsin inhibitors. *Peptides*, **21**, 289-293.

57. Krauland, A., Leitner, V. M. and Bernkop-Schnürch*, A. (2002). Improvement in the in situ gelling properties of deacetylated gellan gum by the immobilization of thiol groups. *J. Pharm. Sci.* under review.

58. Langoth, N., Kalbe, J. and Bernkop-Schnürch*, A. (2002). Development of buccal drug delivery systems based on a thiolated polymer. *Int. J. Pharm.*, under review.

59. Marschütz, M.K. and Bernkop-Schnürch*, A. (2000). Oral peptide drug delivery: Polymer-inhibitor conjugates protecting insulin from enzymatic degradation. *Biomaterials*, **21**, 1499-1507.

60. Marschütz, M.K., Caliceti, P., and Bernkop-Schnürch*, A. (2000) Design and *in vivo* evaluation of an oral delivery system for insulin. *Pharm. Res*, **17**, 1468-1474.

61. Marschütz, M.K., Puttipipatkhachorn, S., and Bernkop-Schnürch*, A. (2001) Design and *in vitro* evaluation of a mucoadhesive oral delivery system for a model (poly)peptide antigen. *Pharmazie*, **56**, 724-729.

62. Marschütz, M.K., Veronese, F.M., and Bernkop-Schnürch*, A. (2001) Influence of the spacer on the inhibitory effect of different polycarbophil-protease inhibitor conjugates. *Eur. J. Pharm. Biopharm.*, **52**, 137-44.

63. Marschütz, M.K., and Bernkop-Schnürch*, A. (2002) Thiolated polymers: Advance in mucoadhesion by use of in-situ crosslinking poly(acrylic acid)-cysteine conjugates. *Eur. J. Pharm. Sci.*, **15**, 387-394.

64. Marschütz, M.K., Zauner, W., Mattner, F., Otava, A., Buschle, M. and Bernkop-Schnürch*, A. (2002) Improvement of the enzymatic stability of a cytotoxic T-lymphocyte epitope model peptide for its oral administration. *Peptides*, in press.

65. Roldo, M., Hornof, M., Caliceti, P. and Bernkop-Schnürch*, A. (2002) Improvement in the mucoadhesive properties of chitosan by derivatisation with 2-iminothiolane. *J. Pharm. Sci.*, under review.

66. Valenta*, C., and Bernkop-Schnürch, A. (1993). Untersuchungen von Kontaminationsrisken bei der Herstellung von magistralen Augentropfen. *ÖAZ,* **47**, 141-143.

67. Valenta*, C., Bernkop-Schnürch, A., and Rigler, H.P. (1996). The anti-staphylococcal effect of nisin in a suitable vehicle, a potential therapy for atopic dermatitis. *J. Pharm. Pharmacol.*, **48**, 988-991.

68. Valenta*, C., Bernkop-Schnürch, A., and Teltscher, C. (1996). Nisin, ein potentielles Konservierungsmittel in topischen Zubereitungen. *Pharmazie,* **51**, 119-122.

69. Valenta*, C., Bernkop-Schnürch, A. and Schwartz, M. (1997) Modification of lysozyme with cinnamaldehyde: A strategy for constructing novel biopreservatives for dermatics. *Int. J. Pharm.*, **148**, 131-137.

70. Valenta*, C., Christen, B., and Bernkop-Schnürch, A. (1998). Chitosan-EDTA Conjugate: A novel polymer for topical used gels. *J. Pharm. Pharmacol.*, **50**, 445-452.

71. Valenta*, C., Schwarz, E.G., and Bernkop-Schnürch, A. (1998). Lysozyme caffeic acid conjugates: possible novel preservatives for dermatics. *Int. J . Pharm.*, **174**, 125-132.

72. Valenta*, C., Nowack, E., and Bernkop-Schnürch, A. (1999). Deoxycholate-Hydrogels: Novel Drug Carrier Systems for Topical Use. *Int. J . Pharm.*, **185**, 103-111.

73. Valenta*, C., Walzer, A., Clausen, A.E., and Bernkop-Schnürch, A. (2001). Thiolated polymers: development and evaluation of transdermal delivery systems for progesterone. *Pharm. Res.*, **18**, 211-216.

74. Valenta*, C., Kast, E.C., Harich, I., and Bernkop-Schnürch, A. (2001). Development and in vitro Evaluation of a Mucoadhesive Vaginal Delivery System for Progesterone. *J. Controlled Release*, **77**, 323-332.

75. Valenta*, C., Marschütz, M., Egyed, Ch., and Bernkop-Schnürch, A. (2002). Evaluation of the inhibitory effect of thiolated poly(acrylates) on vaginal membrane bound aminopeptidase N. *J. Pharm. Pharmacol.*, **54**, 603-610.

76. Walker, G.F., Langoth, N., and Bernkop-Schnürch, A.* (2002). Peptidase activity on the surface of the porcine buccal mucosa. *Int. J. Pharm.*, **233**, 141-147.

Review Arcticles:

1. Bernkop-Schnürch*, A. (1997). Strategien zur peroralen Applikation von Peptid- und Proteinwirkstoffen. *Sci. Pharm.*, **65**, 61-81.

2. Bernkop-Schnürch*, A. (1997). Bioadhäsive Polymere als Hilfsstoffe zur peroralen Applikation von Peptid- und Proteinwirkstoffen. *ÖAZ,* **51**, 490-495.

---

* *corresponding author*

3. Bernkop-Schnürch*, A. (1998). The use of inhibitory agents to overcome the enzymatic barrier to perorally administered therapeutic peptides and proteins. *J. Control. Release,* **52**, 1-16.

4. Bernkop-Schnürch*, A. (1999). Polymer-Inhibitor Conjugates: A Promising Strategy to Overcome the Enzymatic Barrier to Perorally Administered (Poly)Peptide Drugs? *s.t.p. pharma sciences*, **9**, 78-87.

5. Bernkop-Schnürch*, A. (2000). Chitosan and its derivatives: Potential excipients for peroral peptide delivery systems. *Int. J. Pharm.*, **194**, 1-13.

6. Bernkop-Schnürch*, A. (2000). The Use of Multifunctional Polymers for the Noninvasive Peptide and Protein Application. *Expert Opinion Ther. Pat.* **10**, 1357-1366.

7. Bernkop-Schnürch*, A. and Kast, C. (2001). Chemically modified chitosans as enzyme inhibitors. *Advanced Drug Delivery Reviews*, **52**, 127-137.

8. Bernkop-Schnürch*, A. and Walker, G. (2001). Multifunctional matrices for oral peptide delivery. *Crit. Rev. Ther. Drug Carr. Syst.* **18**, 27-70.

9. Bernkop-Schnürch*, A. and Clausen A.E. (2002).Membranes as Targets for Drug Design: Biomembrane Permeability of Peptides: Strategies to Improve their Mucosal Uptake. *Mini Reviews in Medicinal Chemistry*, **2**, 295-305.

Book Contributions:

Bernkop-Schnürch*, A. (2002). Mucoadhesive Polymers In: Polymeric Biomaterials 2nd edition (Ed. Severian Dumitriu) Marcel Dekker, New York.

Patents:

1. Bernkop-Schnürch, A. und Paikl, Ch. (1997). Verfahren zur Herstellung von Chitosan-Ethylendiamintetraacetat Konjugaten. AT Patentschrift 1997-01-21, A 79/97

2. Bernkop-Schnürch, A. and Paikl, Ch. (1998). Chitosan Conjugates with acidic chelate-complex forming agents. WO 09831712A2. National application pending in: US

3. Bernkop-Schnürch, A. (1998). Verfahren zur Verbesserung der Mucoadhäsion von Polymeren sowie deren Herstellung und Verwendung. WO 00/25823. National applications pending in: EP, US, JP, CA, AU, CN, IN

4. Kratzel, M., Hiessböck, R., und Bernkop-Schnürch, A. (1998). Simplifizierte Pepstatin A-Analoga, deren Herstellung und Verwendung. AT Patentschrift 1998-01-23.

5. Bernkop-Schnürch, A., Schuhbauer, H. and Pischel, I. (1999). α-Liponsäure(-Derivate) enthaltende Retardform, German patent application 1999-09-30; PCT-application pending.

6. Kratzel, M. und Bernkop-Schnürch, A. (1999). Valylamide und deren Verwendung als Enzymhemmer. AT Patentschrift 1999-07-09.

7. Bernkop-Schnürch, A. und Clausen, A. (2002). Drug delivery systems for the improvement of paracellular permeation of hydrophilic compounds. Austrian patent application.

Granted Projects:

Bernkop-Schnürch, A.: Thiolisierte Polymere in Peptidwirkstoff-abgabesystemen, FWF-Project (*Nov. 2001 – Sept. 2004; 300.000 Euro*)

Bernkop-Schnürch, A.: Development of Drug Delivery Systems for the Peroral Administration of Peptide and Protein Drugs, *FWF-Project (Jul. 1998 – Oct. 2001; 121,000 Euro)*

Bernkop-Schnürch, A.: Development of Drug Carrier Systems with Improved Mucoadhesive Properties, *FWF-Project (Nov. 1999 – Dec. 2002; 180,000 Euro)*

Bernkop-Schnürch, A.: Entwicklung magensaftresistenter Arzneiformen für die perorale Applikation von Peptid- und Proteinwirkstoffen, *Projekt der Hochschuljubiläumsstiftung der Stadt Wien (Jan. 1999 – Jun. 2000; 2,500 Euro)*

Wugeditsch, Th., and Bernkop-Schnürch, A.: Entwicklung und Evaluierung von Ocularia basierend auf neuartigen mukoadhäsiven Polymeren, *FWF-Impuls-Project (Aug. 2000 – Jul. 2002; 75,000 Euro)*

Bernkop-Schnürch, A.:Thiolated Polymers in Peptide Drug Delivery Systems, *FWF-Project (Nov. 2001 – Oct. 2004; 300,000 Euro)*

Bernkop-Schnürch, A.: Der Einfluß von Thiolteilstrukturen auf die parazelluläre Permeation von Peptidwirkstoffen, *Projekt der Hochschuljubiläumsstiftung der Stadt Wien (Jan. 2002 – Jun. 2002; 2,100 Euro)*

Industrial Projects:

Mucos Emulsionsgesellschaft, Leberstr. 96, A-1110 Vienna, Austria
(*Development of oral protein delivery systems,* ***Project leader:*** *Mag. B. LOTZ*)

Degussa Trostberg, Dr.-A.-Frank-Str. 32, D-83308 Trostberg, Germany
(*Development of sustained release systems for α-lipoic acid,* ***Project leader:*** *Dr. H. SCHUHBAUER*)

Degussa Trostberg, Dr.-A.-Frank-Str. 32, D-83308 Trostberg, Germany
(*Development of colon delivery system for α-lipoic acid,* ***Project leader:*** *Dr. H. SCHUHBAUER*)

Croma-Pharma, Industriezeile 6, A-2100 Leobendorf, Austria
(*Development of viscoelastic polymers for ophthalmic use,* ***Project leader:*** *Mag. M. PRINZ*)

Elan Pharmaceutical Technologies, Biotechnology Building, Trinity College, Dublin 2, Ireland
(*Generation and evaluation of novel permeation enhancing systems,* ***Project leader:*** *Dr. A. RAOOF*)

Bayer AG, D-42096 Wuppertal, Germany
(*Development of buccal delivery systems for peptide drugs,* ***Project leader:*** *Dr. J. KALBE*)

Bayer AG, D-42096 Wuppertal, Germany
(*Development of a nasal delivery system for Vardenafil HCl,* ***Project leader:*** *Dr. J. KALBE*)

Serono, Instituto di Ricerca Cesare Serono SpA, Via di Valle Caia, 22 – 00040 –Ardea, Italy
(*Development of Nasal Drug Delivery Systems for Beta Sheet Breaker Peptides,* ***Project leader***: Dr. Maria Dorly del CURTO)

Serono, Instituto di Ricerca Cesare Serono SpA, Via di Valle Caia, 22 – 00040 –Ardea, Italy
(In vivo Evaluation of Different Oral Drug Delivery Systems for Antide, ***Project lead r***: Dr. Maria Dorly del CURTO)

Trommsdorff GmbH& Co. KG, 52475 Alsdorf, Germany
(*Prüfung der mukoadhäsiven Eigenschaften von MTDA und MTDA-Lysinat,* ***Project leader***: Dr. Rudy SUSILO)

Collaborations:

Univ. Prof. Dr. Udo M. Losert
Institut für Biomedizinische Forschung
Allgemeines Krankenhaus Wien / AKH Leitstelle 1Q
Währinger Gürtel 18-20
A-1090 Vienna, Austria
(*Tissue engineering by utilizing thiolated chitosans*)

Univ. Prof. Dr. Rainer Oberbauer
Univ.-Klinik für Innere Medizin III
Abteilung von: Fachbereich Innere Medizin
Währinger Gürtel 18-20
A-1090 Vienna, Austria
(*Clinical studies with novel sustained release delivery systems*)

Univ. Prof. Dr. Annick Ludwig
Laboratory of Pharmaceutical Technology and Biopharmacy
University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium
(*Development of ophthalmic drug delivery systems*)

Dr. S. Senel
Hacettepe University, Faculty of Pharmacy
Department of Pharmaceutical Technology
Ankara, Turkey
(*The use of thiolated chitosan in buccal delivery systems*)

Univ. Prof. Dr. Paolo Caliceti
Department of Pharmaceutical Sciences
Faculty of Pharmacy
University of Padua
Via F. Marzolo, 535131 Padua - Italy
(*Development of oral insulin delivery systems*)

Univ.Prof. Dr. Ivo Schmerold
Veterinärmedizinische Universität Wien
Institut für Pharmakologie und Toxikologie
Veterinärplatz 1
A - 1020 Vienna, Austria
(*Evaluation of mucoadhesive delivery systems in pigs*)

Dr. Alexander Becherer
Univ.-Klinik für Nuklearmedizin
Allgemeines Krankenhaus Wien / AKH Leitstelle 1Q

Währinger Gürtel 18-20
A-1090 Vienna, Austria
(*Szintigraphic determination of the GI-transit time of mucoadhesive delivery systems in human volunteers*)

Prizes awarded:

HERBA-Award 1997 (3,000 Euro)

Research-Award of the City of Vienna 1999 (3,000 Euro)

Eurand-Award 2000 (1,500 Euro)

Best of Biotech Award 2001 Phase I (725 Euro)

Best of Biotech Award 2001 Phase II (1,450 Euro)

MBPW Award 2002 Phase I-III (26,750 Euro)

Oral Presentations:

Bernkop-Schnürch, A. (1991) The Use of *Escherichia coli* Adhesive Antigen K99 for Drug Carrier Systems. Institute of Microbiology and Genetic, University of Vienna.

Bernkop-Schnürch, A. (1992) Searching for Peptide Ligands with an Epitope Library. Institute of Microbiology and Genetic, University of Vienna.

Bernkop-Schnürch, A. (1995) Ansätze zu peroralen (Poly)peptid Applikationssystemen. Institute of Pharmaceutical Technology, University of Vienna.

Bernkop-Schnürch, A. (1996) Entwicklung eines bioadhesiven Arzneistoffabgabesystems zur peroralen Ulkustherapie mittels EGF. Institute of Pharmaceutical Technology, University of Vienna.

Bernkop-Schnürch, A. (1997) Enzyminhibitoren als Hilfsstoffe zur peroralen Applikation von Peptid- und Proteinwirkstoffen. ÖPHG Congress, Vienna.

Bernkop-Schnürch, A. (1997) Strategien zur peroralen Applikation von Peptid- und Proteinwirkstoffen. HERBA-Award, Vienna.

Bernkop-Schnürch, A. (1997) Strategies for the peroral administration of insulin. Institute of Pharmaceutical Chemistry, University of Padova, Italy.

Bernkop-Schnürch, A. (1997) Intestinal peptide and protein delivery: Coadministration of inhibitory agents. 2nd Central European Symposium on Pharmaceutical Technology, Portoroz, Slovenia.

Bernkop-Schnürch, A. (1998) Development of drug delivery systems with protective effect towards GI proteases. 2nd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Paris, France.

Bernkop-Schnürch, A. (1998) Entwicklung bioadhäsiver Polymere zur peroralen Applikation von Peptid- und Proteinwirkstoffen, Ludwig Maximilians Universität Munich, Germany.

Bernkop-Schnürch, A. (1998) Bioadhäsiver Polymere zur peroralen Applikation von Peptid- und Proteinwirkstoffen, Freie Universität Berlin, Germany.

Bernkop-Schnürch, A. (1998) Synthese von Polymeren zur peroralen Applikation von Peptid- und Proteinwirkstoffen, AKH Vienna.

Bernkop-Schnürch, A., Schwarz, V., and Thaler, S. (1999) Improved Mucoadhesive Properties of Polycarbophil by the Covalent Attachment of Cysteine, 26th Int. Symp. on Controlled Release of Bioact. Mat., Boston, USA.

Bernkop-Schnürch, A. (1999) Thiolated polymers: a new generation of mucoadhesive polymers, 3rd Central European Symposium on Pharmaceutical Technology, Portoroz, Slovenia.

Bernkop-Schnürch, A. (1999) Enzyme-Inhibitors, Elan Pharmaceutical Technologies, Dublin, Ireland.

Bernkop-Schnürch, A. (1999) Novel Delivery Systems for alpha-Lipoic Acid, 2nd Dietary Supplement Symposium Trostberg, Germany

Bernkop-Schnürch, A., Marschütz, M. and Clausen, A. (2000) Design of Polymeric Conjugates for Improved Oral Delivery, 4th International Symposium on Polymer Therapeutics, University of London, London, U.K.

Bernkop-Schnürch, A. (2000) The Use of Thiolated Polymers in Oral Drug Delivery, 27th Int. Symp. on Controlled Release of Bioact. Mat., Paris, France.

Bernkop-Schnürch, A. (2000) Polymeric Conjugates in Oral Drug Delivery – An Overview, Elan Pharmaceutical Technologies, Dublin, Ireland.

Bernkop-Schnürch, A. (2000) New Approaches in the Development of Drug Delivery Systems, Cardiff, UK.

Bernkop-Schnürch, A. (2000) Thiolated (Poly)acrylates, CPhI Congress, Milano, Italy.

Bernkop-Schnürch, A. (2000) Der Einsatz chemisch modifizierter Polymere als Wirkstoffträgermatrix, München, Deutschland

Bernkop-Schnürch, A. (2001) Das LADME Prinzip aus Pharmazeutisch Technologischer Sicht, Institute of Pharmaceutical Chemistry, Vienna, Austria

Bernkop-Schnürch, A. (2001) Thiolated Polymers: A New Platform Technology for Drug Delivery Systems? Serono, Turin, Italy

Bernkop-Schnürch, A. (2001) Thiomere: Eine neue Generation polymerer Hilfsstoffe, Jena, Germany

Kast C., Hornof M. and Bernkop-Schnürch A., (2001) Einfluß von kovalent gebundenen Thiolgruppen auf die mukoadhäsiven und viskoelastischen Eigenschaften von Chitosan. 6. Österreichischer Kohlenhydratworkshop, Vienna, Austria

Kast C., Frick W., Kapeller B., Eberl H., Falkner E., Macfelda K., Bernkop-Schnürch A. and Losert U. (2001) Chitosan-thioglycolic acid conjugate as scaffold in tissue engineering, 4th Central European Symposium on Pharmaceutical Technology, Vienna, Austria

Hornof M., Kast C. and Bernkop-Schnürch A. (2001) Improvement of the mucoadhesive and viscoelastic properties of chitosan by the introduction of thiol moieties, 4th Central European Symposium on Pharmaceutical Technology, Vienna, Austria

Poster Presentations:

Bernkop-Schnürch, A., Gabor, F., Szostak, M. und Lubitz, W. (1992) Gentechnologische Herstellung Bioadhäsiver Arzneistoffträger. ÖPHG Congress, Vienna.

Bernkop-Schnürch, A., Gabor, F. und Spiegl, P. (1995) Bioadhäsiva: Isolierung und Charakterisierung von *E. coli* K99 Fimbrien. ÖPHG Congress, Innsbruck, Austria.

Bernkop-Schnürch, A., Paikl, Ch., Valenta, C. und Spiegl, P. (1997) Entwicklung eines bioadhäsiven Polymers mit komplexierenden Eigenschaften für zweiwertige Kationen. ÖPHG Congress, Vienna.

Bernkop-Schnürch, A., Bratengeyer, I. und Spiegl, P. (1997) Entwicklung von Freigabesystemen zur peroralen Peptid- und Proteinapplikation mit Schutz vor tryptischem Verdau. ÖPHG Congress, Vienna.

Bernkop-Schnürch, A., Apprich, I. und Spiegl, P. (1997) Synthese und Evaluierung eines Polyacrylsäure-Chymostatin Konjugates. ÖPHG Congress, Vienna.

Bernkop-Schnürch, A. and Scerbe-Saiko, A. (1997) Intestinal peptide and protein delivery: Synthesis and evaluation of a chitosan-inhibitor conjugate. 2nd Central European Symposium on Pharmaceutical Technology, Portoroz, Slovenia

Kratzel, M., Hiessböck, R. and Bernkop-Schnürch, A. (1997) Peroral administration of peptide and protein drugs - synthesis of novel pepstatin analogues as pepsin inhibitors. 2nd Central European Symposium on Pharmaceutical Technology, Portoroz, Slovenia

Kratzel, M., Hartmann, P. und Bernkop-Schnürch, A. (1997) Synthese und Evaluierung von neuen Pepsin-Inhibitoren als Adjuvantien zur peroralen Applikation von Peptid- und Proteinwirkstoffen. GDCH Congress, Vienna.

Valenta, C. and Bernkop-Schnürch, A. (1997) Chitosan-EDTA conjugate: a novel polymer for topical used gels. 2nd Central European Symposium on Pharmaceutical Technology, Portoroz, Slovenia

Valenta, C., Bernkop-Schnürch, A., Krist, S. und Spiegl, P. (1997) Erweiterung des antimikrobiellen Wirkungsspektrums von Lysozym durch Kopplung mit Kaffeesäure oder Zimtsäure. ÖPHG Congress, Vienna.

Bernkop-Schnürch, A., and Pasta, M. (1998) Intestinal Peptide and Protein Delivery: Synthesis and Evaluation of Chitosan-EDTA - Bowman-Birk Inhibitor Conjugates. The 17th Pharmaceutical Technology Conference and Exhibition, Dublin, Ireland.

Bernkop-Schnürch, A., Humenberger, C., and Valenta, C. (1998) Influence of Ionic Crosslinkers on Cohesiveness of Bioadhesive Polymers used as (Poly)peptide Drug Carrier Matrices. The 17th Pharmaceutical Technology Conference and Exhibition, Dublin, Ireland.

Valenta, C., Bernkop-Schnürch, A., and Schwarz, E. (1998) Lysozyme-Caffeic Acid Conjugates: Possible Novel Preservatives For Dermatics. 2nd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Paris, France.

Bernkop-Schnürch, A. and Scerbe-Saiko, A. (1999) Development of a bioadhesive drug delivery system for orally administered therapeutic peptides and proteins. World Congress of Pharmacy and Pharmaceutical Sciences '99, Barcelone, Spain.

Clausen, A., Marschütz, M., Riegler, M. and Bernkop-Schnürch, A. (1999) Thiolated polycarbophil as penetration enhancer for (poly)peptide drugs, 26th Int. Symp. on Controlled Release of Bioact. Mat., Boston, USA.

Valenta, C., Gilge, B. and Bernkop-Schnürch, A. (1999) Influence of the Gastric Fluid on Mucoadhesive Polymeric Carrier Systems for Therapeutic (Poly)Peptides, 26th Int. Symp. on Controlled Release of Bioact. Mat., Boston, USA.

Valenta, C., Nowack, E. and Bernkop-Schnürch, A. (1999) Deoxycholate-Hydrogels: Novel Drug Carrier Systems for Topical Use, 26th Int. Symp. on Controlled Release of Bioact. Mat., Boston, USA.

Clausen, A., Marschütz, M., Steininger, S. and Bernkop-Schnürch, A. (1999) Method to control the stability of matrix tablets based on thiolated polycarbophil, 3rd Central European Symposium on Pharmaceutical Technology, Portoroz, Slovenia

Bernkop-Schnürch, A., Hoffer, M., Kirchmayer, R. and Kratzel, M. (1999) A drug delivery system with protective effect towards pepsinic degradation - development, synthesis and *in vitro* evaluation, 3rd Central European Symposium on Pharmaceutical Technology, Portoroz, Slovenia

Marschütz, M., Clausen, A., and Bernkop-Schnürch, A. (1999) Development of a CMC-inhibitor conjugate protecting insulin from enzymatic attack in an artificial intestinal fluid, 3rd Central European Symposium on Pharmaceutical Technology, Portoroz, Slovenia

Kratzel, M., and Bernkop-Schnürch, A. (1999) Valaminole—neue simplifizierte Pepstatin A—Analoga: Synthese und Evaluierung als Pepsin-Inhibitoren, ÖPHG-Tagung, Innsbruck, Austria

Clausen, A.E. , Marschütz, M., Kast, C., Freudl, J. and Bernkop-Schnürch, A. (2000) Design and in vitro Evaluation of a Drug Carrier Matrix Based on a Thiolated Polymer, Bioencapsulation: Innovation and Technologies, Vienna, Austria

Clausen, A.E., Marschütz, M. and Bernkop-Schnürch, A. (2000) Permeation Enhancing Effect of Thiolated Carboxymethylcellulose, 27th Int. Symp. on Controlled Release of Bioact. Mat., Paris, France.

Freudl, J., Clausen, A.E. and Bernkop-Schnürch, A. (2000) Thiolated Polycarbophil: A Promising Enhancer for the Paracellular Route of Drug Absorption? 27th Int. Symp. on Controlled Release of Bioact. Mat., Paris, France.

Kast, C.E., Freudl, J. and Bernkop-Schnürch, A. (2000) Mucoadhesive Thiolated Polymers: Synthesis and in vitro Evaluation of Chitosan-Thiogycolic Acid Conjugates, 27th Int. Symp. on Controlled Release of Bioact. Mat., Paris, France.

Marschütz, M.K., Caliceti, P., Clausen, A.E. and Bernkop-Schnürch, A. (2000) Design and *in vivo* Evaluation of an oral Delivery System for Insulin, 27th Int. Symp. on Controlled Release of Bioact. Mat., Paris, France.

Bernkop-Schnürch, A., Clausen, A.E. and Kast, C.E. (2000) Stabilization of Polymeric Drug Carrier Systems via Disulfide Bond Formation, 27th Int. Symp. on Controlled Release of Bioact. Mat., Paris, France.

Bernkop-Schnürch, A., Clausen, A.E. and Kast, C.E. (2000) The Use of Thiomers as Multifunctional Excipients in Drug Delivery, 10th Internat. Pharm. Technol. Symposium, Istanbul, Turkey.

Clausen, A.E., Hnatyszyn, M., Kast, C.E., Marschütz, M.K., and Bernkop-Schnürch, A. (2000) Thiolated carboxymethylcellulose: a new excipient for enhanced hydrophylic therapeutic absorption. 10th Internat. Pharm. Technol. Symposium, Istanbul, Turkey.

Kast, C.E., Clausen, A.E., Marschütz, M.K., Bernkop-Schnürch, A. (2000) Biodegradation of chitosan-thioglycolic acid conjugates by lysozyme. 10th Internat. Pharm. Technol. Symposium, Istanbul, Turkey.

Marschütz, M.K., Veronese, F.M., Clausen, A.E., and Bernkop-Schnürch, A. (2000) Synthesis and *in vitro* evaluation of a polycarbophil-PEG-

inhibitor conjugate—a novel excipient for oral peptide drug delivery?. 10th Internat. Pharm. Technol. Symposium, Istanbul, Turkey.

Kast C. and Bernkop-Schnürch A. (2001) Synthesis and in vitro evaluation of polycarbophil-cysteamine conjugates. 4th Central European Symposium on Pharmaceutical Technology, Vienna, Austria.

Kast C., Senel S., Özalp M., Hincal A., Hornof M. and Bernkop-Schnürch A. (2001) Antimyrobial activity of chitosan-thioglycolic acid conjugates. 4th Central European Symposium on Pharmaceutical Technology, Vienna, Austria.

Langoth N., Walker G. and Bernkop-Schnürch A. (2001) Aminopeptidase activity on the surface of the porcine buccal mucosa. 4th Central European Symposium on Pharmaceutical Technology, Vienna, Austria.

Marschütz M. and Bernkop-Schnürch A. (2001) Interaction of a poly(acrylic acid)-cysteine conjugate with the intestinal mucus gel layer. 4th Central European Symposium on Pharmaceutical Technology, Vienna, Austria.

Walker G., Langoth N. and Bernkop-Schnürch A. (2001) A new in vitro system for measuring the metabolic barrier of the buccal epithelium. 4th Central European Symposium on Pharmaceutical Technology, Vienna, Austria.

Member of the Editorial Board for:
European Journal of Pharmaceutics and Biopharmaceutics
s.t.p. pharma sciences

Referee for:

Pharmaceutical Research
Journal of Controlled Release
Journal of Pharmaceutical Sciences
International Journal of Pharmaceutics
European Journal of Pharmaceutical Sciences
European Journal of Pharmaceutics and Biopharmaceutics
Scientia Pharmaceutica
Biomacromolecules

M3# 98/338 report number 98/338/c

Polymers with thiol groups: a new generation of mucoadhesive polymers?

by Bernkop-Schnürch, Schwarz V, Steiniger S

General comments

This is a well written article* making use of the cleavage of disulfide bonds by compounds containing thiols as acetylcysteine. This well known reaction is exploited to increase unspecific mucoadhesion by cleaving the disulfide bridge of mucus with acetylcysteine coupled to polycarbophil with the result that polycarbophil is covalently linked to mucus. This idea is brillant and there is some evidence given in the paper that it really works although the experimental in vitro circumstances especially if (synthetic) mucus is involved are very complex for a sound interpretation. The referee therefore suggests to include in this article simple ex-vivo methods as e.g. measuring of residence times of polymer-cysteine conjugates beads compared to polycarbophil beads in freshly isolated gut of rats or pigs as e.g. described by Lehr et al. in STP Pharma 5 (1989) 857-862 to have more evidence of improved mucoadhesion under physiological conditions.
Such a proof would also allow to omit the questionmark at the end of the title because then enough evidence is given that polymers containing thiol groups may be a new generation of mucoadhesive polymers if there are no toxicological contraints to use them.

* (the English could be improved by the desk editor and there are some minor typing errors).